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#18 Appeal Brief (3)

33,359-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants : Stephen A. Udem et al.

Application No.: 09/508,913

Filed : March 16, 2000

For : Attenuated Respiratory Syncytial Viruses

Examiner : U. Winkler

Group Art Unit : 1648 Confirmation No.: 3738

Customer No. : 25291

July 23, 2003

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Hon. Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

APPELLANTS' BRIEF UNDER 37 C.F.R. 1.192(a)

Sir:

Appellants filed their Notice of Appeal on December 23, 2002, in response to the Final Rejection mailed August 27, 2002. This brief is accompanied by the fee

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CERTIFICATION UNDER 37 C.F.R. 1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EU673382284US addressed to the Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

July 23, 2003
Date

Alan M. Gordon

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required under 37 C.F.R. 1.17(c). Appellants are also submitting herewith a petition for a five month extension of time, together with the fee required under 37 C.F.R. 1.136. With the extension, this brief is due on July 23, 2003.

An oral hearing was requested in the notice of appeal. That request was accompanied by the fee required under 37 C.F.R. 1.17(d).

In accordance with 37 C.F.R. 1.192(a), this brief is submitted in triplicate.

Real Party in Interest

The assignee of this application is Wyeth Holdings Corporation (formerly known as American Cyanamid Company), which is a wholly-owned subsidiary of Wyeth (formerly known as American Home Products Corporation).

Related Appeals and Interferences

The appeals in U.S. application numbers 09/269,367 and 09/646,756 raise similar issues to the appeal involving this application.

Status of Claims

Originally, Claims 1-14 were filed with this application. Subsequently, Claims 2, and 4-14 were cancelled (see next section). Thus, the pending claims are Claims 1 and 3. The Examiner has rejected all the pending claims. All of the pending claims are being appealed. The text of Claims 1 and 3 on appeal is set forth in the Appendix hereto.

Claims 1 and 3 are independent claims.

Status of Amendments

The Examiner issued a non-final rejection mailed December 5, 2001. On June 5, 2002, Appellants filed an Amendment which cancelled Claims 2, and 4-14 and amended Claim 1. The Examiner entered this Amendment in the final rejection mailed August 27, 2002.

Summary of Invention

Human respiratory syncytial virus (RSV) is a nonsegm nted, negative-sense, single stranded envelop d RNA virus. RSV b longs to the Subfamily Pneumovirinae and the

genus *Pneumovirus* (see page 1, lines 14-17 of the specification). Two major subgroups of human RSV, designated A and B, have been identified based on reactivities of the F and G surface glycoproteins with monoclonal antibodies (page 2, lines 23-24 and page 3, lines 11-13 of the specification).

RSV is the primary cause of serious viral pneumonia and bronchiolitis in infants and young children. Serious disease, i.e., lower respiratory tract disease (LRD), is most prevalent in infants less than six months of age. It most commonly occurs in the nonimmune infant's first exposure to RSV. RSV additionally is associated with asthma and hyperreactive airways and it is a significant cause of mortality in "high risk" children with bronchopulmonary dysplasia and congenital heart disease (CHD). It is also one of the common viral respiratory infections predisposing to otitis media in children. In adults, RSV generally presents as uncomplicated upper respiratory illness; however, in the elderly it rivals influenza as a predisposing factor in the development of serious LRD, particularly bacterial bronchitis and pneumonia (page 25, lines 6-22 of the specification).

The invention which is the subject of the claims of the application in this appeal is the identification of a series of specific attenuating mutations in the RNA polymerase gene of RSV subgroup B, the insertion of one or more of those mutations into recombinant forms of RSV, and the use of those recombinant mutant RSVs as vaccines (page 9, lines 14-30 of the specification).

Prior to the invention, a variety of approaches had been used in attempts to develop vaccines against RSV, including the use of: (1) purified individual viral protein vaccines (subunit vaccines); (2) inactivated whole virus preparations; and (3) live, attenuated viruses (page 4, lines 21-25 of the specification).

Subunit vaccines have the desirable feature of being pure, definable and relatively easily produced in abundance by various means, including recombinant DNA expression methods. To date, with the notable exception of hepatitis B surface antigen, viral subunit vaccines have generally only elicited short-lived and/or inadequate immunity, particularly in naive recipients (page 4, lines 26-33 of the specification).

Formalin inactivated whole virus preparations of polio (IPV) and hepatitis A have proven safe and efficacious. In contrast, immunization with similarly inactivated whole RSV vaccines elicited unfavorable immune responses and/or response profiles which predisposed vaccinees to exaggerated or aberrant disease when subsequently confronted with the natural or "wild-type" virus (page 4, line 34-page 5, line 6 of the specification).

Early attempts (1966) to vaccinate young children used a parenterally administered formalin-inactivated RSV vaccine. Unfortunately, several field trials of this vaccine revealed serious adverse reactions -- the development of a severe illness with unusual features following subsequent natural infection with RSV. It has been suggested that this formalinized RSV antigen elicited an abnormal or unbalanced immune response profile, predisposing the vaccinee to RSV disease (page 5, lines 7-16 of the specification).

Thereafter, biologically-derived, live, attenuated RSV vaccine candidates were generated by cold passage or chemical mutagenesis, that is, by non-recombinant means. These RSV strains were found to have r duced virul nce in

seropositive adults. Unfortunately, they proved either over- or underattenuated when given to seronegative infants; in some cases, they also were found to lack genetic stability. Another vaccination approach using parenteral administration of live virus was ineffective and efforts along this line were discontinued (page 7, line 2-11 of the specification).

Appropriately attenuated live derivatives of wild-type viruses offer a distinct advantage as vaccine candidates. As live, replicating agents, they initiate infection in recipients during which viral gene products are expressed, processed and presented in the context of the vaccinee's specific MHC class I and II molecules, eliciting humoral and cell-mediated immune responses, as well as the coordinate cytokine patterns, which parallel the protective immune profile of survivors of natural infection (page 7, lines 19-28 of the specification).

While live, attenuated viruses have highly desirable characteristics as vaccine candidates, they have proven to be difficult to develop. The crux of the difficulty lies in the need to isolate a derivative of the wild-typ virus which has lost its diseas -producing

potential (i.e., virulence), while retaining sufficient replication competence to infect the recipient and elicit the desired immune response profile in adequate abundance (page 8, lines 6-16 of the specification).

Historically, this delicate balance between virulence and attenuation has been achieved by serial passage of a wild-type viral isolate through different host tissues or cells under varying growth conditions (such as temperature). This process presumably favors the growth of viral variants (mutants), some of which have the favorable characteristic of attenuation. Occasionally, further attenuation is achieved through chemical mutagenesis as well (page 8, lines 15-23 of the specification).

This propagation/passage scheme typically leads to the emergence of virus derivatives which are temperature sensitive, cold-adapted and/or altered in their host range -- one or all of which are changes from the wild-type, disease-causing viruses -- i.e., changes that may be associated with attenuation (page 8, lines 24-29 of the specification).

At the time biologically d rived mutant RSVs were generated, in the late 1980s and early 1990s, those of

ordinary skill in the art did not have the ability to readily sequence 15,000 base long genomes of RSV. At the same time, those in the art also did not have the ability to manipulate RSV recombinantly to generate viral strains having defined mutations which could then be assessed for a desired attenuating phenotype.

Appellants utilized two distinct technologies which were developed after Randolph U.S. patent 5,932,222 (cited by the Examiner as an allegedly anticipatory reference against the instant application on appeal; see discussion below): Sequencing of long viral genomes such as RSV, and reverse genetics ("rescue") for manipulating non-segmented, negative-stranded RNA viruses such as RSV. Appellants were able to sequence the various RSV B strains described in Randolph U.S., analyze the sequence distinctions between wild-type viruses and biologically-derived RSV vaccine strains, and identify mutations in various regions, including the RNA polymerase gene, which contribute to desirable attenuating phenotypes. Appellants' specification then describes techniques so that a person of ordinary skill in the art can ass ss rescued strains

containing Appellants' claimed mutations for suitability for vaccine use.

Two such biologically-derived RSV strains, designated 2B33F and 2B20L, were the subject of commonly-assigned Randolph U.S. patent 5,932,222 (cited by the Examiner as an allegedly anticipatory reference against the instant application on appeal; see discussion below). However, in the absence of sequence information for those two mutant strains, the absence of sequence information for the wild-type parental 2B strain, no comparison of the wild-type and mutant sequences was possible, and the attenuating mutations of this virus could not be ascertained.

Rational vaccine design would be assisted by a better understanding of RSV, in particular, by the identification of the virally encoded determinants of virulence as well as those genomic changes which are responsible for attenuation (page 8, lines 30-34 of the specification).

The objects of the invention are achieved by the generation and isolation of recombinantly-generated, att nuated, human RSV subgroup B having at least one

attenuating mutation in the RNA polymerase gene (page 9, lines 14-18 of the specification).

In the case of human RSV subgroup B, Appellants have identified, by sequence comparisons of biologically-derived mutant viruses and a wild-type pathogenic virus, a series of attenuating mutations in the RNA polymerase gene, wherein at least one attenuating mutation in the RNA polymerase gene is selected from the group consisting of nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 353 (arginine → lysine), 451 (lysine → arginine), 1229 (aspartic acid → asparagine), 2029 (threonine → isoleucine) and 2050 (asparagine → aspartic acid), wherein the numbering of the amino acid residues is based upon the numbering of the amino acid residues in the RSV wild-type strain RSV 2B (SEQ ID NO:2) (page 9, lines 19-26 and page 33, line 35-page 34, line 6 of the specification; Claim 1 on appeal).

In summary, the invention comprises the identification of changes in the RNA polymerase (L) gene of an RSV subgroup B virus, which result in attenuation of the virus while retaining sufficient ability of the virus to replicate. Attenuation is optimized by rational mutations

of the polymerase gene, which provide the desired balance of replication efficiency and immunogenicity: so that the virus vaccine is no longer able to produce disease, yet retains its capacity to infect the vaccinee's cells, to express sufficiently abundant gene products to elicit the full spectrum and profile of desirable immune responses, and to reproduce and disseminate sufficiently to maximize the abundance of the immune response elicited (page 19, lines 16-28 of the specification).

In another embodiment of this invention, these attenuated human respiratory syncytial subgroup B viruses are used to prepare vaccines which elicit a protective immune response against the wild-type form of the virus (page 9, lines 27-30 of the specification).

In yet another embodiment of this invention, an isolated, positive strand, antigenomic message sense nucleic acid molecule (or an isolated, negative strand genomic sense nucleic acid molecule) having the complete viral nucleotide sequence (whether of wild-type virus or virus attenuated by non-recombinant means) is manipulated by introducing one or more of the attenuating mutations d scribed in this application to generate an isolated, recombinantly-generated

attenuated human RSV subgroup B. Each attenuated virus is then used to prepare vaccines which elicit a protective immune response against the wild-type form of each virus (page 9, line 31-page 10, line 8 of the specification).

The one or more mutations to the RNA polymerase gene of RSV subgroup B are introduced by standard recombinant DNA methods into a DNA copy of the viral genome (page 20, lines 28-30 of the specification). Infectious clones or particles containing these attenuating mutations are generated using the cDNA "rescue" system, which has been applied to a variety of viruses, including RSV (page 20, line 33-page 21, line 8 of the specification). The rescue system did not exist at the time the application was filed which issued as Randolph U.S. patent 5,932,222. The rescue system used to obtain recombinant viruses is described in detail at page 21, line 9-page 23, line 13 of Appellants' specification.

The rescue system provides a composition which comprises a transcription vector comprising an isolated nucleic acid molecule encoding a genome or antigenome of an RSV subgroup B having at least one attenuating mutation in the RNA polymerase gene, together with at least one

expression vector which comprises at least one isolated nucleic acid molecule encoding the trans-acting N, P, L and M2 proteins necessary for encapsidation, transcription and replication. Host cells are then transformed or transfected with the at least two vectors just described. The host cells are cultured under conditions which permit the co-expression of these vectors so as to produce the infectious attenuated virus (page 23, lines 16-30 of the specification).

The rescued infectious RSV is then tested for its desired phenotype (temperature sensitivity, cold adaptation, plaque morphology, and transcription and replication attenuation), first by *in vitro* means (page 23, lines 31-34 of the specification).

The identification of attenuating mutations in the RNA polymerase gene of the RSV subgroup B viruses of this invention involved an analysis of the nucleotide sequences of various wild-type, vaccine and revertant RSV strains. In particular, the emphasis was on the RNA polymerase gene (page 32, lines 24-29 of the specification).

The nucleotide sequences (in positive strand, antigenomic, message sense) of various wild-type, vaccine

and revertant RSV subgroup B strains are set forth as follows with reference to the appropriate SEQ ID NOS. contained herein:

Virus	Nucleotide Sequence	Genome
Wild-Type		Length
2B	SEQ ID NO:1	15218
18537	SEQ ID NO:3	15229
Vaccine		
2B33F	SEQ ID NO:5	15219
2B20L	SEQ ID NO:7	15219
Revertant		
2B33F TS(+)	SEQ ID NO:9	15219
2B20L TS(+)	SEQ ID NO:11	15219

Translation of the RNA polymerase gene for these strains starts with the codons as listed at page 33, lines 24-33 of the specification; the translation stop codons for these strains are also as listed at page 33, lines 24-33 of the specification. The translated L protein is 2,166 amino acids long for each strain (page 33, lines 18-19 of the specification).

As detailed in Example 8 (especially Tables 21 and 22) below, the key potentially att nuating sites for the L protein of RSV subgroup B are as follows: amino acid residues 353 (arginine → lysine), 451 (lysine → arginin),

1229 (aspartic acid → asparagine), 2029 (threonine → isoleucine) and 2050 (asparagine → aspartic acid). It is understood that the nucleotide changes responsible for these amino acid changes are not limited to those set forth in Example 8 below; all changes in nucleotides which result in codons which are translated into these amino acids are within the scope of this invention (page 33, line 35-page 34, line 11 of the specification).

The attenuated RSV subgroup B viruses of this invention exhibit a substantial reduction of virulence compared to wild-type viruses which infect human and animal hosts. The extent of attenuation is such that symptoms of infection will not arise in most immunized individuals, but the virus will retain sufficient replication competence to be infectious in and elicit the desired immune response profile in the vaccinee (page 34, lines 12-19 of the specification).

Issues

The issues on this appeal are whether:

(1) Claim 1 is unpatentable under 35 U.S.C. 112, first paragraph;

(2) Claims 1 and 3 are unpatentable under 35 U.S.C. 102(e) as being anticipated by Randolph et al. U.S. patent 5,932,222 ("Randolph U.S.");

(3) Claims 1 and 3 are unpatentable under 35 U.S.C. 102(b) as anticipated by Randolph et al. EP 0 567 100 A1 ("Randolph EP");

(4) Claims 1 and 3 are unpatentable under the judicially created doctrine of obviousness-type double patenting over Claims 7-10 of Randolph U.S.

Grouping of Claims

The claims do not stand or fall together. As discussed below, the Examiner has rejected only Claim 1 under 35 U.S.C. 112, first paragraph. The Examiner did not impose such a rejection with respect to Claim 3. Both Claims 1 and 3 are subject to the Examiner's prior art rejections.

Argument

Claim 1 Is Fully Enabled By The Specification And Thus Does Comply With 35 U.S.C. 112, First Paragraph

The Examiner has rejected Claim 1 under 35 U.S.C. 112, first paragraph, as allegedly not being enabled by the specification for an attenuated virus by making a single mutation in the RNA polymerase gene. The Examiner concedes that the specification is enabling for attenuated viral mutants that have multiple mutations (Paper No. 15, page 3).

Appellants respectfully submit that a close reading of the specification fully supports claims to isolated, recombinantly-generated, attenuated, RSV subgroup B having at least one defined attenuating mutation in the RNA polymerase (L) gene. This is particularly true with regard to the mutations resulting in changes in amino acid residues 451 and 2050.

The specification recites at page 55, lines 2-16:

> "In 2B33F, a mutation at nucleotide position 9853 (A → G) leading to a coding change in L protein at amino acid 451 (Lys → Arg) is clearly associated with the *ts* and attenuation phenotypes. Reversion at this site alone in the 2B33F TS(+) 5a strain is responsible for complete restoration of growth at 39°C (Table 23) and partial reversion in att nuation in animals. This association of *ts* was also support d by partial sequence analys s of

> six additional "full *ts* revertants" (designated 4a, 3b, pp2, 3A, 5a, 5A) isolated from cell culture and from chimps, in which only the nucleotide 9853 mutation reverted (Tables 24-26) (note that one AGM (African Green Monkey) isolate which reverted at 9853 only partially reverted in *ts* phenotype)."

Thus, the attenuating nature of the mutation at amino acid residue 451 has been demonstrated.

The specification further recites at page 55, lines 22-33:

> "In 2B20L, a mutation at base 14,649 (A → G) leading to a coding change in the L protein (amino acid position 2,050, Asn → Asp) appears to be associated with the *ts* and attenuation phenotypes. This aspartic acid at the amino acid 2050 invariably reverts back (Asp → Asn) in TS(+) revertants or changes to a different amino acid (Asp → Val) by nucleotide substitution at position 14,650 (A → T) (Tables 22, 25). The above observation is based on complete sequence analysis on the TS(+) revertant R1 and partial sequence of several additional TS(+) revertants (R2, R4A, R7A, R8A) at selected regions (Table 25)."

Thus, the attenuating nature of the mutation at amino acid residue 2050 has been demonstrated.

The sequence comparisons reported in Tables 21 and 22, together with the *in vitro* and *in vivo* experiments and the sequence analyses of Tables 23-26, further support the importance of each of the mutations claimed by Appellants.

In addition, the specification further provides details as to how a person skilled in the art of recombinant negative-stranded RNA viruses would introduce one or more claimed mutations in the polymerase (page 20, lines 3-33), rescue a claimed virus containing one or more listed mutations in the polymerase (page 22, line 11, through page 23, line 30), test the virus to confirm the presence of the desired attenuated phenotype (page 23, lines 31 through 34), and then conduct challenge experiments with an appropriate animal model (page 23, line 35 through page 24, line 17).

Appellants submit that the skilled person can follow the teachings of the specification to ascertain whether one or more specific mutations confer sufficient attenuation to a virus so as to lack pathogenicity while preventing disease.

Appellants have identified sequence differences between wild-type viruses which cause disease and biologically-derived viruses which are attenuated. By dissecting these differences, and by using the rescue system, the skilled person is able to construct recombinant viruses with on or more of th claimed attenuating mutations in the RNA polym rase gene.

Thus, for the reasons stated above, Appellants respectfully submit that the cited portions of the specification enable a person of ordinary skill in this art to practice the claimed invention without undue experimentation, such that the specification enables Claim 1 under U.S.C. 112, first paragraph.

Claims 1 and 3 Are Not Anticipated By Randolph U.S. Under 35 U.S.C. 102(e)

The Examiner has rejected Claims 1 and 3 under 35 U.S.C. 102(e) as allegedly anticipated by Randolph U.S. In making this rejection, the Examiner has not taken into account the nature of the invention, nor the relevant law.

Appellants were the first to analyze the sequence of both RSV subgroup B wild-type and vaccine strains with respect to the polymerase gene. Without both a knowledge of the sequences themselves and an analysis of the differences between the sequences, it is impossible to identify attenuating mutations in a vaccine strain.

Randolph U.S. discloses the existence of the 2B wild-typ and the 2B33F and 2B20L vaccine strains. Howev r,

Randolph U.S. does not provide any sequence information about these strains.

Therefore, Randolph U.S. cannot teach a difference between a wild-type strain and a vaccine strain at one or more of amino acids 353, 451, 1229, 2029 and 2050 in the polymerase of RSV subgroup B, nor does Randolph U.S. teach that any of these mutations are attenuating. For these reasons, Randolph U.S. cannot anticipate Appellants' claims, because, according to the Court of Appeals for the Federal Circuit's decision in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990):

> "For a prior art reference to anticipate in terms of 35 U.S.C. 102, every element of the claimed invention must be identically shown in a single reference."

The Examiner nonetheless contends that the depositing of the 2B33F and 2B20L vaccine strains (but not the 2B wild-type strain) means that Randolph U.S. inherently possesses the sequences claimed by Appellants.

Appellants respectfully submit that this is an incorrect statement of the law. A distinction must be drawn between the physical characteristics of a product and its structure. In the case of a virus containing one or more

attenuating mutations, the physical characteristics include the phenotype of the virus, such as attenuation, growth and immunogenicity. In contrast, the structure is its genotype, the specific nucleotide sequence which encodes a specific amino acid sequence.

The two cases cited by the Examiner are not relevant on this point. In re Best involved a patent application directed to a catalyst. Both the application and the cited prior art described the catalyst in terms of physical, not structural characteristics. In contrast to In re Best, here the prior art (Randolph U.S.) described the virus only in terms of physical characteristics, while this application on appeal describes the virus in terms of structural characteristics. In re Schreiber is even less relevant. That case involved a medical device, not a chemical or biological composition.

Far more relevant is the decision by the Court of Appeals for the Federal Circuit in Minnesota Mining and Mfg. Co. v. Chemique Inc., 64 USPQ2d 1270 (Fed.Cir. 2002). The Board is directed to the following passage in this case:

> "For prior art to anticipate because it is 'known', the knowl dge must be publicly

> accessible. Woodland Trust, 148 F.3d at 1370, 47 USPQ2d at 1365. In addition, the disclosure must be sufficient to enable one with ordinary skill in the art to practice the invention. In re Borst, 345 F.2d at 855, 145 USPQ at 557."

Continental Can Co. USA Inc. v. Monsanto Co., 948 F2d 1264, 20 USPQ2d 1746 (Fed.Cir. 1991) is also relevant:

> "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (20 USPQ2d at 1749)

Here, such extrinsic evidence is lacking.

Furthermore, as stated in Finnegan Corp. v. ITC, 51 USPQ2D 1001 (Fed.Cir. 1999), evidence of inherency must be "clear and convincing":

> "As such, because one skilled in the art would not necessarily recognize that nonresonance ejection is disclosed in the Jefferts article, the evidence is not clear and convincing that the Jefferts article inherently anticipates claims 1 and 8." (51 USPQ2d at 1009)

Additionally, as stated in Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc., (Fed.Cir. 1995):

> "Anticipation, however, requires identity of invention; the claimed invention, as described in appropriately construed claims, must be the same as that of the refer nce, in order to anticipate.

> Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1267, 20 USPQ2d 1746, 1748 (Fed.Cir. 1991). See also In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed.Cir. 1990) ('the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it'). (33 USPQ2d at 1498)

Furthermore, there is another requirement which must be met in order for a prior art reference to qualify as anticipating -- as stated in Akzo N.V. v. International Trade Commission, 1 USPQ2d 1241 (Fed.Cir. 1986):

> "In addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public." (1 USPQ2d at 1245)

By the same reasoning, it should be held here that Randolph U.S. also did not provide an adequate written description of the structure, that is, the sequence of the RSV B strains, by virtue of the deposited materials plus characterization of their phenotypic properties. Therefore, it is incorrect to state that Randolph U.S. inherently possessed the nucleotide sequences claimed in this application, and thus Randolph U.S. did not enable the claimed invention in this application on appeal.

A USPTO Examiner Has Already Held That Randolph U.S. Is Not Enabling For Nucleic Acid Sequences Under 35 U.S.C. 102(e)

Appellants will now demonstrate that another Examiner in the United States Patent and Trademark Office has held that the specification of the U.S. patent application from which Randolph U.S. claimed priority was not enabling for claims directed to nucleic acid molecules encoding RSV mutants, because no DNA sequences were disclosed. This serves to negate the Examiner's argument about the claims in this instant application on appeal.

Randolph U.S. claimed priority from U.S. patent application serial number 07/871,420 ("Randolph '420 application"), filed April 22, 1992, which included the following claims 12-17:

> 12. A nucleic acid molecule encoding the cold-adapted mutant respiratory syncytial virus of Claim 1.
> 13. A nucleic acid molecule encoding immunogenic polypeptide of Claim 7.
> 14. A nucleic acid molecule encoding the chimeric polypeptide of Claim 10.
> 15. A nucleic acid molecule of Claims 12 to 14, wherein the nucleic acid molecule is a DNA molecule.
> 16. The nucleic acid molecule of Claim 15, wherein the DNA molecule is a cDNA molecule or an RNA molecule.
> 17. The nucl ic acid molecule of Claim 15 or 16 operatively linked to a promoter of transcription.

In response, United States Patent and Trademark Examiner Pandya on January 7, 1993, issued a first Office Action in which the Examiner, among other things, rejected Claims 12-17 of the Randolph '420 application under 35 U.S.C. 112, first paragraph, and stated:

> "The specification is not enabled for the recited nucleic acid molecules encoding the cold adapted mutant RSV and any associated polypeptides. The specification has discussed at length, the art recognized methods of recombinant DNA technology, determination of sequence regions encoding viral genome, expression vectors, etc. (pages 30-43). However, the specification has failed to disclose any specific DNA sequences encoding for the claimed cold adapted RSV or any associated polypeptides."[1]

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[1] Copies of the postcard stamped by the PTO, page 1 and the claims of the Randolph '420 application, and the Examiner's January 7, 1993 Office Action are attached to this Brief. In the interest of completeness, Appellants provide the following information. Randolph did not file a response to the Office Action in the '420 application; instead, she filed continuation-in-part application serial number 08/059,444 on May 7, 1993, which ultimately issued as the Randolph U.S. patent cited by the Examiner in this instant appeal. Randolph U.S. as filed again presented nucleic acid claims. However, those claims were the subject of a restriction requirement, were not elected and were cancelled. Subsequently, Randolph filed divisional application serial number 08/441,630 on May 15, 1995 ("Randolph '630 application"). Claims 18-21 of the Randolph '630 application were directed to RSV nucleic acid sequences, as were claims 25-41 added by amendment of February 26, 1996. On May 29, 1996, Examiner Park rejected Claims 18-21 and 25-41 under 35 U.S.C. 112, first paragraph, on grounds similar to those raised by the Examiner in the instant application on appeal, rather than on the grounds raised by Examiner Pandya in the Randolph '420 application. This does not, how ver, change the fact or reasoning of Examiner Pandya's rejection. Randolph did not respond to the Office Action and the Randolph '630 application became abandoned.

Appellants (and the public) should be able to rely on Examiner Pandya's determination that the Randolph '420 application did not enable claims to sequences of RSV nucleic acid molecules. For the Examiner in the instant appeal to contend otherwise is inconsistent and does not foster public trust in the U.S. patent system. For this reason alone, the Examiner's determination that Claims 1 and 3 are anticipated by Randolph U.S. should be reversed.

But there are additional reasons why the Examiner's rejection under 102(e) should not stand. The Examiner relies on the deposit of the RSV B vaccine strains 2B33F and 2B20L in Randolph U.S. to support the (improper) inherency argument. However, the Examiner did not mention that Randolph U.S. did not deposit the corresponding wild-type 2B strain.

Even assuming for the sake of argument that the deposits of the 2B33F and 2B20L strains enabled the sequence of those strains (which Appellants vigorously dispute), without a deposit of the 2B strain there would be no basis for enablement of the wild-type strain. The only way the exist nce of an att nuating mutation at Appellants' claimed loci of the RSV RNA polymeras gene could b ascertained is

where the sequences of all of the 2B, 2B33F and 2B20L strains are available, are compared, and key attenuating loci identified based on sequence differences. This was not the case here because the 2B sequence was not available in Randolph U.S.

For the reasons stated above, the claims are not anticipated by Randolph U.S. Nor are these claims rendered obvious by Randolph U.S.

Claims 1 and 3 Are Not Anticipated By Randolph EP Under 35 U.S.C. 102(b)

The Examiner has rejected Claims 1 and 3 under 35 U.S.C. 102(b) as allegedly anticipated by Randolph EP. Randolph EP claims the same priority as Randolph U.S. and has essentially the same disclosure. Therefore, Randolph EP cannot anticipate the claims, for all the reasons set forth above with respect to Randolph U.S.

Claims 1 and 3 Are Not Subject To An Obviousness-Type Double Patenting Rejection Over Claims 7-10 Of Randolph U.S.

Finally, the Examiner has rejected Claims 1 and 3 as allegedly unpatentable under the judicially created

doctrine of obviousness-type double patenting over Claims 7-10 of Randolph U.S.

Appellants note first that this ground was raised for the first time in the Examiner's August 27, 2002 final rejection. The Examiner nowhere recited that this ground of rejection was necessitated by the June 5, 2002 Amendment. Thus, the Examiner has not proceeded in compliance with MPEP 706.07(a), "Final Rejection, When Proper on Second Action", which reads in pertinent part:

> "Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that in neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p)."

Here, there has been no showing made by the Examiner that the Amendment necessitated this obviousness-type double patenting new ground of rejection - nor is there a basis for such a showing. (The portion of the MPEP section relating to an IDS is not applicable here.) Appellants' Amendment, which merely combined the limitations of Claims 1 and 2, and added clarifying language, could in no way have necessitated th new ground of rejection.

Appellants submit therefore that it was inappropriate for the Examiner to raise this obviousness-type double patenting rejection in the final rejection. If the Examiner wishes to maintain this ground of rejection, the finality of the rejection should be withdrawn. Alternatively, the Examiner should withdraw this ground of rejection in order to maintain the finality of the rejection.

Notwithstanding the foregoing, Appellants will now demonstrate on the merits that Claims 1 and 3 are not obvious over Claims 7-10 of Randolph U.S.

Claims 7-10 of Randolph U.S. all reference mutant RSV strains which are biologically-derived and which are derived from the RSV 2B wild-type virus; Claims 8 and 10 further recite the specific 2B33F (VR2364) and 2B20L (VR2368) strains. The Examiner again relies on the deposit of those two strains as the inherent basis for disclosure of the sequences of those strains.

For the same reasons set forth with respect to the Section 102 discussion above, Appellants submit that the sequences of th 2B33F and 2B20L strains are not inh rently disclosed by Randolph U.S., even with the deposit of those

strains. (Nor is the sequence of the wild-type 2B strain disclosed in Randolph U.S., and that strain was not deposited in Randolph U.S., such that no sequence comparisons were possible between the wild-type and mutant strains.)

Even if inherently disclosed - which Appellants vigorously dispute - Appellants respectfully submit that the Examiner's rejection on the ground of obviousness based on inherency of sequences in Randolph U.S. is not appropriate as a matter of law. As was stated in W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303, 314 (Fed.Cir. 1983):

"Inherency and obviousness are distinct concepts." Consequently, as stated in In re Spormann and Heinke, 150 USPQ 449, 452 (CCPA 1966):

> "[T]he inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."

In re Spormann was quoted with approval by the Court of Appeals for the Federal Circuit in In re Rijckaert, 28 USPQ2d 1955, 1957 (Fed.Cir. 1993).

Therefore, for the reasons stated above,

Appellants respectfully submit that pending Claims 1 and 3 are not properly subject to an obviousness-type double patenting rejection over Claims 7-10 of Randolph U.S., and this ground of rejection should be reversed.

Conclusion

Appellants respectfully submit that, for the reasons discussed above, Claim 1 on appeal complies with 35 U.S.C. 112, first paragraph. Appellants further submit that Claims 1 and 3 on appeal are not anticipated by or obvious over the prior art cited by the Examiner. For the reasons set forth herein, Appellants respectfully urge that the Decision of the Examiner should be reversed and Claims 1 and 3 be allowed.

Respectfully submitted,

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Patent Law Department
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Attorney for Appellants

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Appendix

Claims on Appeal

1. An isolated, recombinantly-generated, attenuated, human respiratory syncytial virus (RSV) subgroup B having at least one attenuating mutation in the RNA polymerase gene, wherein the at least one attenuating mutation in the RNA polymerase gene is selected from the group consisting of nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 353 (arginine → lysine), 451 (lysine → arginine), 1229 (aspartic acid → asparagine), 2029 (threonine → isoleucine) and 2050 (asparagine → aspartic acid), wherein the numbering of the amino acid residues is based upon the numbering of the amino acid residues in the RSV wild-type strain RSV 2B (SEQ ID NO:2).

3. A vaccine comprising an isolated, recombinantly-generated, attenuated RSV subgroup B according to Claim 1 and a physiologically acceptable carrier.

NEW APPLICATION BEING FILED HEREWITH

EXPRESS MAIL NO.
GB65293535XUS

31,822-00
Antoinette F. Konski

In re application of: Valerie Bruce Randolf and
Joan Coflan Crowley

For: MUTANT RESPIRATORY SYNCYTIAL VIRUS (RSV),
VACCINES CONTAINING SAME AND METHODS OF USE

Enclosed: Transmittal Letter (triplicates)
81 pages of Specification, 3 pages of
Claims (28 in total), 1 page of Abstract
and 7 Sheets of Informal Drawings
(triplicates)

Mailed: April 22, 1992

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07/871420 Mailed: April 22, 1992

Case Number: 31,822-00

Mutant Respiratory Syncytial Virus (RSV), Vaccines Containing Same And Methods of Use

BACKGROUND OF THE INVENTION

Throughout this application, various references are referred to in parenthesis to more fully describe the state of the art to which this invention pertains. Full bibliographic information for each citation is found at the end of the specification, immediately preceding the claims. The disclosures of these references are hereby incorporated by reference into the present disclosure.

Respiratory syncytial virus (RSV), a member of the paramyxovirus family, is the leading cause of viral pneumonia and bronchiolitis in infants and young children and is responsible for an estimated 95,000 hospitalizations and 4,500 deaths per year in the United States (IOM report, 1985; Hall and McBride, 1991; McIntosh and Chanock, 1990). Serious disease is most prevalent in infants 6 weeks to 6 months of age and in children with certain underlying illnesses (e.g. immunodeficiencies, congenital heart disease and bronchopulmonary dysplasia). Two major subgroups of RSV have been identified, A and B, as well as antigenic variants within each subgroup (Anderson et al, 1985; Mufson et al, 1985). Multiple variants of each subgroup have been found to cocirculate in epidemics which occur annually during late fall, winter, and spring months (Anderson et al, 1991). Most children

What is claimed is:

1. A cold adapted mutant respiratory syncytial virus (RSV).

2. A cold adapted mutant respiratory syncytial virus subgroup A.

3. A cold adapted mutant respiratory syncytial virus subgroup B.

4. A cold adapted mutant respiratory syncytial virus subgroup A of Claim 2, wherein the mutant virus is selected from the group consisting of 3Ap20E, 3Ap20F and 3Ap28F.

5. A cold adapted mutant respiratory syncytial virus subgroup B of Claim 3, wherein the mutant virus is selected from the group consisting of 2Bp33F, 2Bp24G, 2Bp20L and 2Bp34L.

6. A pharmaceutical composition comprising the mutant RSV of Claim 1 and a pharmaceutically acceptable carrier.

7. Purified immunogenic polypeptide isolated from the mutant RSV of Claim 1.

8. The purified immunogenic polypeptide of Claim 7, wherein the polypeptide is selected from the group consisting of L, F, G, M, M2(22K), P, SH, 1B, 1C and N.

9. A pharmaceutical composition comprising the immunogenic polypeptide of Claim 7 and a pharmaceutically acceptable carrier.

10. A chimeric polypeptide comprising one or more of the polypeptides of Claim 8.

11. A pharmaceutical composition comprising the chimeric polypeptide of Claim 10 and a pharmaceutically acceptable carrier.

12. A nucleic acid molecule encoding the cold -adapted mutant respiratory synctial virus of Claim 1.

13. A nucleic acid molecule encoding immunogenic polypeptide of Claim 7.

14. A nucleic acid molecule encoding the chimeric polypeptide of Claim 10.

15. A nucleic acid molecule of Claims 12 to 14, wherein the nucleic acid molecule is a DNA molecule.

16. The nucleic acid molecule of Claim 15, wherein the DNA molecule is a cDNA molecule or an RNA molecule.

17. The nucleic acid molecule of Claim 15 or 16 operatively linked to a promoter of transcription.

18. An expression vector comprising the nucleic acid molecule of Claim 17.

19. A host cell comprising the nucleic acid molecule of Claims 12, 13, 14 or 17.

20. A recombinant polypeptide encoded by the nucleic acid molecule of Claim 13 or 14.

21. A recombinant virus encoded by the nucleic acid molecule of Claim 12.

22. A pharmaceutical composition comprising the recombinant polypeptide of Claim 20 and a pharmaceutically acceptable carrier.

23. A pharmaceutical composition comprising the nucleic acid molecule of Claims 13, 17 or 18, and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition comprising the recombinant virus of Claim 21, and a pharmaceutically acceptable carrier.

25. A method of vaccinating against respiratory syncytial viral infection in a subject comprising administering to the subject an effective immunizing amount of the pharmaceutical composition of Claims 6, 9, 11 or 22 to 24.

26. The method of Claim 25, wherein the subject is a mammal.

27. A method of producing a recombinant polypeptide which comprises growing the host cell of Claim 18 under suitable conditions and purifying the recombinant polypeptide so produced.

28. A method of producing an attenuated RSV which comprises growing the host cell of Claim 19 under suitable conditions such that recombinant virus are produced in the host cell.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/871,420	04/21/92	RANDOLPH	V 31.822-00

EXAMINER
PANDYA, D

ART UNIT	PAPER NUMBER
1813	7

DATE MAILED: 01/07/93

ANTOINETTE F. KONSKI
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

PLEASE ADD TO SCHEDULE
April 7, 1993

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire THREE month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 12-19, 27-28 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 12-19, 27-28 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-11, 20-26, drawn to virus derived compositions that promote immunization when administered to a living body , classified in Class 424, subclass 89.

II. Claims 12-19, 27-28, drawn to nucleic acids and associated expression products, classified in Class 536, subclass 27 and Class 935.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are not related by function. The virus of Group I is mutually different in characteristic from the nucleotides of Group II.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

If Applicant elects Invention Group I, Applicant is further required to elect a species as set forth below:

Claim 8 is generic to a plurality of disclosed patentably distinct species comprising polypeptides located in envelope; Inner envelope; nucleocapsid and surface regions of RSV. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

During a telephone conversation with Estelle Tsevdos (Reg. No. 31,145) on December 01, 1992 a provisional election was made with traverse to prosecute the invention of Group II, claims 12-19, 27-28 . Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-11, 20-26 withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

The disclosure is objected to because of the following informalities:

On page 47, line 35 of the disclosure, the results of the study are incorrectly referenced to non-existent Table 16, the examiner believes this should read "Table 12".

Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The disclosure is not fully enabled for the recited cold adapted mutant respiratory syncytial virus as claimed. The disclosure recites that samples of the mutant RSV pertaining to the instant invention have been deposited under the provisions of Budapest Treaty (page 15, lines 6-15), however it is unclear if the deposits have meet all the criteria set forth in 37 CFR 1.801-1.809.

Applicant's are reminded that without a publicly available deposit of the mutant RSV, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Note that the best mode is not satisfied by a written disclosure unless the exact embodiment is reasonably reproducible from the disclosure.

If the deposits were made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each state. Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with criteria set forth in 37 CFR 1.801 - 1.809, items 1-3 regarding availability and permanency of deposits, assurance of compliance is required. Such assurances may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number averring:

a. during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

b. all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

c. the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

d. the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As a possible means of completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

The specification is not enabled for the recited nucleic acid molecules encoding the cold adapted mutant RSV and any associated polypeptides. The specification has discussed, in length, the art recognized methods of recombinant DNA technology, determination of sequence regions encoding viral genome, expression vectors etc. (page 30 - 43). However, the specification has failed to disclose any specific DNA sequences encoding for the claimed cold adapted RSV or any associated polypeptides. In the absence of this guidance, the examiner holds such an invention to be highly unpredictable. Also, in the absence of any working examples utilizing recombinantly expressed mutant RSV or immunogenic polypeptides, one of ordinary skill in the art would not be able to practice the invention without undue experimentation.

Claims 12-19, 27-28 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim 12-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-14 are dependent on non-elected claims. The subject matter of the pertinent non-elected claims needs to be incorporated into these claims.

In claim 12, the recited "cold adapted RSV" reads on any prior art cold adapted RSV's presently known. The applicants have admitted that the cold adaption of RSV is strain dependent (page 49, line 4). The applicants have further disclosed mutant strains pertaining to the instant invention have been deposited (page 15) it is required that the mutant cold adapted RSV are clearly distinguished over prior art by showing specific characteristics, such as cold adaption temperatures, ATCC designations etc, to render this claim definite.

In claim 14, the term "chimeric" is confusing in the context in which it is used. The examiner understands the term to refer to a composite of two or more unrelated species. However in this case all the polypeptides are all isolated from a single source i.e the mutant RSV, if the applicants intends for a composite of more than one nucleic acid molecule, encoding more than one polypeptide, then the claim such be amended to reflect as such.

Claim 15, contains unacceptable multiple dependent claim language, and should be amended to include terms in the form of "as in one of the claims 12 to 14" or "as in any of claims 12-14" as appropriate,
see M.P.E.P 608.01 (n).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 12-19, 27-28 rejected under 35 U.S.C. § 103 as being unpatentable over Wertz et al., in view of Youngner et al., Palese et al., and Collins et al.

Wertz et al., provides methods for producing recombinantly expressed polypeptides of RSV and methods of their use.
In a review of the prior art, the authors explain the limitations of cold adapted RSV viruses as vaccines in terms of limited infectivity and poor immunogenicity, (col 2, line 40-44). The authors teach the advantage of using recombinantly expressed proteins is to avoid exposure of patients to inactivated or attenuated virus (col 3, line 40, presumably the same advantages as would be conferred by the instant invention. The reference then teaches the art recognized methods of expression of recombinant RSV proteins, by the use of vectors, host cells etc (col 5-13), in the same manner as claimed in the instant invention. The complete nucleotide sequences of various viral proteins are also disclosed, thereby anticipating the possibility of producing chimeric polypeptides as claimed in the instant invention (see charts 12-16, for example).

Wertz et al., differs from the instant invention as not teaching any utility for cold adapted mutant RSV viruses or any methods for recombinantly expressing such a virus.

Palese et al., teaches the methods of recombinant expression of viruses containing enveloped single-stranded RNA, such as paramyxovirus (RSV belongs to this family), and othhomyxoviridae family (comprising influenza viruses), see col 3, line 30 and claim 1, for instance. The author explains that recombinantly expressed virus are advantageous for use where a lot of strain variability exists and that this method allows for the construction of a large repertoire of viruses (col 8, line 40-55), this is consistent with the intended advantages conferred by the recombinant expression of the attenuated mutant RSV as disclosed in the instant invention.

Collins et al., presents another possible method of expressing active recombinantly expressed RSV viruses by complementing synthetic RNA with viral proteins and expression using cDNA (see abstract). The author reflects on a long felt need for the ability to produce live virus from cDNA for RSV as this would provide a means of producing attenuated vaccine strains (page 9663, first paragraph, RHS).

Youngner et al., teaches the methods and use of cold adapted influenza virus. The effectiveness of cold adapted viruses as anti-viral agents as shown by their inhibition ability, is similar to that of the mutant RSV as claimed in the instant invention (see col 2, line 2-5, for example). The applicant's have also admitted that methods for producing and using cold adapted RSV as well known in the art(page 4, line 3).
Therefore, in view of the collective teachings of Palese et al., Collins et al., and Younger et al., it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Wertz et al., to include the means of expression of cold adapted mutant attenuated RSV using DNA or RNA molecules encoding for the virus, especially in view of a long felt need for such a virus as taught by Collins et al., furthermore a virus produced by this method would be expected to produce a safer vaccine composition for example, as it would be easier to probe the viral genome and mutations like substitution, deletions or insertions could be safely evaluated either singly or in combination. Also, these methods would result in unlimited supplies of polypeptides and viruses that can be used to prepare pharmaceutical compositions.

Thus, the claimed invention, as a whole, is clearly prima facie obvious, especially in evidence to the contrary.

The examiner is citing the following prior art of interest:
Gelb et al., teaches the technique of cold adaption of an avian bronchitis virus.

Prior art made of record and not used is considered pertinent to the applicant's disclosure.

No claims are allowed.

Any inquiry concerning this communication should be directed to Dilip Pandya, whose telephone number is (703) 308-3995.

Any inquiry of a general nature should be directed to the Group receptionist, whose telephone number is (703) 308-0916.

Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers should conform with the notice published in the official Gazette, 1096 OG 30 (November 15, 1989), the CM1 Fax Center number is (703) 308-4227.

Dilip P. Pandya
December 17, 1992.

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180